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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/258,132	02/26/1999	PHILIP GOELET	04990.0007.U	3407

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/258,132	GOELET ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64 and 66-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64 and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 3, 2005. Applicant's arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. This action is made final.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 64, 66, 67, and 69-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO) 90/11372, October 4, 1990; cited in the IDS).

It is noted that EP 0412883A1 claims priority to application 8910802, which issued as and is identical in content to FR 2,650,840. An English translation of FR 2,650,840 was filed in the IDS of June 8, 1999.

Cohen teaches a method for determining the identity of one or more nucleotide bases in a nucleic acid molecule wherein the method comprises contacting a single-stranded nucleic acid sample with an oligonucleotide primer to form a duplex between the primer and complementary target nucleic acids present in the sample, wherein the primer hybridizes immediately 3' of the nucleotide to be determined; contacting the duplexes with a solution containing four different terminators, each terminator labeled with a different detectable moiety; extending the primer with the terminator, and determining the identity of the incorporated terminator to thereby determine the identity of the nucleotide base (see pages 4 and 5). Cohen (page 6) states that "if the four blocking bases are marked by means of different markers, the four blocking nucleotides are advantageously detected at the same time." In the method of Cohen, only terminator nucleotides are present in the extension reaction – the reaction does not contain dATP, dCTP, dGTP or dTTP (see, for instance, Example 1). Cohen does not teach using performing the primer extension reaction using multiple primers, each comprising a different affinity moiety.

However, Davis teaches a method for determining the identity of one or more nucleotide bases in a nucleic acid molecule wherein the method comprises contacting a single stranded nucleic acid molecule with an oligonucleotide primer to form a duplex between the primer and complementary target nucleic acids; contacting the duplexes

with a solution containing labeled dNTPs, labeled with a different detectable moiety; extending the primer with the dNTPs such that if the primer is perfectly complementary with the target nucleic acid, an extension product is formed, but if the primer contains a mismatch at or near the 3' end of the primer, an extension product is not formed, and detecting the presence of an extension product in order to determine the identity of a nucleotide base (see pages 3-4). Davis teaches that the identity of multiple nucleotides can be determined simultaneously by using a mixture of different oligonucleotides, each oligonucleotide comprising a unique tail (i.e., affinity moiety). Following the extension reaction, the primer extension/target nucleic acid complex is denatured, and the primer extension product is hybridized to a solid support having bound thereto sequences complementary to the primer tail. The unique tail allows for the primers to be immobilized at specific locations on the support (see pages 4-5). Davis teaches that the use of multiple primers, with different tail sequences allows for the simultaneous analysis of multiple sequences and improves the speed and sensitivity of the detection method (see page 21).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have used multiple primers, each having a different tail (i.e., each comprising a different affinity moiety) and to have separated the primer extension products from the reaction medium by contacting the extension products with a solid support having immobilized thereon a capture probe complementary to the tail sequence (i.e., an affinity group complementary to the affinity moiety of the primer) in order to have accomplished the objectives set

forth by Davis of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

With respect to claim 66, Cohen teaches that the terminator (or "blocking nucleotide") is a dideoxynucleotide (see page 5). With respect to claim 67, Cohen teaches that the terminator comprises one or more of ddATP, ddCTP, ddGTP or ddTTP (see pages 7 and 8). With respect to claims 69 and 70, Cohen teaches that the terminator may be labeled with a fluorophore, or chromophore, isotope, enzyme or antibody (see page 5).

RESPONSE TO ARGUMENTS:

In the response filed March 3, 2005, Applicants traversed this rejection by stating that Cohen teaches away from the claimed invention. Applicants point to page 3 of the Cohen reference as teaching that immobilization of nucleic acids on a membrane is a disadvantage of the method of Southern blotting and the method of Mundy (U.S. Patent No. 4,656,127). It is argued that the ordinary artisan would recognize that the method of Davis is an equivalent technique requiring immobilization of the nucleic acid and that the ordinary artisan would recognize that the method of Davis shared the disadvantages of previously known techniques requiring immobilization onto a membrane. Thereby, Applicants conclude that Cohen teaches away from the "the hypothetical combination."

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection for the following reasons. First, it is acknowledged that Cohen (page 3) teaches that "By selecting suitable hybridization and rinsing conditions (specific for each system), hybridization by means of marked

oligonucleotides can be achieved only in case of perfect equivalence (the difference of a single nucleotide, particularly at the site of the mutation, results in destabilization of the hybridization). However, these various techniques all have a certain number of disadvantages: - the temperature conditions are difficult to master to achieve suitable hybridization; - the mandatory presence of a restriction site may be required; - the nucleic acid is immobilized on a membrane (Southern blot). " Accordingly, it is agreed that Cohen teaches away from using Southern blot hybridization techniques to detect single nucleotide variations.

However, the method of Southern is substantially different from the method of Davis and the ordinary artisan would not in fact view these methods as equivalents. The method of Southern relies solely on the selection of suitable hybridization conditions to distinguish between nucleic acids having a single nucleotide difference. Further, in conventional Southern blotting techniques, the sample nucleic acid is irreversibly bound to a membrane via baking or UV crosslinking. In comparison, the method of Davis does not rely on the difficult selection of appropriate hybridization conditions to identify the presence of a single nucleotide variation. Rather, the detection of a single nucleotide variation is accomplished via a primer extension reaction. This primer extension reaction is similar to that of the present invention, with the exception that the extension reaction utilizes labeled dNTPs, rather than labeled ddNTPs. Also, the method of Davis does not require irreversible immobilization of target nucleic acids onto a solid support. Rather, the method of Davis requires reversible immobilization of primer extension products onto a support via binding of an affinity reagent. The original target nucleic

acid is separated from the primer extension reaction by denaturation and can be reanalyzed if necessary. The immobilization step in Davis does not require baking or UV crosslinking since the primer extension product is immobilized by a hybridization reaction between the primer's unique tail (affinity moiety) and the capture probe bound to the solid support. Thereby, the immobilized primer extension product can be removed from the support by denaturation. It is important to emphasize that the step of hybridizing the primer extension product to the support in the method of Davis is significantly different from the step of hybridizing the target nucleic to a probe in the method of Southern. Standard hybridization conditions can be employed in the method of Davis for hybridizing the primer extension product to an immobilized capture probe, whereas in the method of Southern, the entire detection process relies on the selection of a suitable hybridization condition which will allow the probe to hybridize only if it is perfectly complementary to the target nucleic acid. In summary, as compared to Southern, the method of Davis does not require irreversible immobilization of the target nucleic, and does not rely solely on the hybridization of the immobilized target nucleic acid to a probe as a means for detecting the single nucleotide variation. Accordingly, while Cohen teaches away from irreversibly immobilizing a target nucleic acid and directly detecting a single nucleotide variation by hybridization of a target nucleic acid to a probe, there is nothing in Cohen which teaches away from reversibly immobilizing the primer extension product as a means for distinguishing between multiple primer extension products.

It is also important to note that Davis and Cohen are analogous art since both the method of Davis and the method of Cohen rely on performing a primer extension reaction to detect a single nucleotide variation. On the other hand, Cohen and Southern do not rely on similar techniques to accomplish the detection of a single nucleotide variation, since Cohen teaches detecting a single nucleotide variation using a primer extension reaction and Southern teaches detecting a single nucleotide variation using a hybridization reaction.

For the reasons stated above, it is maintained that Cohen and Davis when considered as a whole would have lead the ordinary artisan to the claimed invention. As discussed in the above rejection, Davis teaches that the immobilization of primer extension products to a solid support via an affinity moiety allows for the use of multiple distinct primers simultaneously. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have used multiple primers, each having an affinity moiety and to have separated the primer extension products from the reaction medium by contacting the extension products with a solid support in order to have accomplished the objectives set forth by Davis of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

3. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO 90/11372, October 4, 1990; cited in the IDS) and Prober (U.S. Patent NO. 5,332,666).

The teachings of Cohen and Davis are presented above. The combined references do not teach using a terminator that comprises arabinoside triphosphate.

However, Prober teaches methods for determining a nucleotide sequence wherein the method comprises performing a primer extension reaction using a terminator. Prober teaches that the terminator may contain an arabinose as the sugar group and provides a number of examples of terminators comprising an arabinoside triphosphate (see column 18).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have a terminator comprising an arabinoside triphosphate because this would have provided an equally effective terminator for the extension reaction and for determining the identity of a nucleotide in a target nucleic acid.

RESPONSE TO ARGUMENTS:

In the response filed March 3, 2005, Applicants traversed this rejection for the same reasons as set forth in paragraph 2 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

4. Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO 90/11372, October 4, 1990; cited in the IDS) and Tabor (U.S. Patent NO. 4,962,020; cited in the IDS).

The teachings of Cohen and Davis are presented above. The combined references do not teach including pyrophosphatase in the primer extension medium.

However, Tabor (columns 15-16) teaches including pyrophosphatase in primer extension reactions. The reference teaches that pyrophosphatase removes pyrophosphate which builds up during extension reactions. Specifically, Tabor (column 14) teaches that in the presence of pyrophosphate, DNA polymerase will add pyrophosphate to the 3' terminal nucleotide, causing the release of dideoxynucleoside 5'-triphosphates. As stated by Tabor (column 15, lines 1-2), "This reaction has the effect of removing the block at the 3' terminus."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Cohen so as to have included pyrophosphatase in the reaction medium in order to have achieved the expected benefit of eliminating pyrophosphorolysis activity of DNA polymerase and thereby reducing the probability that the labeled terminator would be removed and that unlabeled dideoxynucleotides would be released into the reaction medium. Thereby, the ordinary artisan would have been motivated to have include pyrophosphatase in the extension reaction in order to have ensured the accuracy and sensitivity of the method for determining the identity of a nucleotide.

RESPONSE TO ARGUMENTS:

In the response filed March 3, 2005, Applicants traversed this rejection for the same reasons as set forth in paragraph 2 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Carla Myers
May 17, 2005

CARLA J. MYERS
PRIMARY EXAMINER